UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/760,274	01/12/2001	John Sinden	GJE-21D2	3086

23557 7590 05/25/2004

SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
2421 N.W. 41ST STREET
SUITE A-1
GAINESVILLE, FL 326066669

EXAMINER	
WILSON, MICHAEL C	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 05/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/760,274	SINDEN ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *57,58,60-62 and 76-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *57,58,60-62 and 76-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2-27-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 2-23-04 have been fully considered but they are not persuasive.

Claims 1-48, 59 and 68-75 have been canceled. Claims 76-86 have been added. Claims 57, 58, 60-62, 64 and 76-86 are pending and under consideration in the instant office action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

The information disclosure statement filed 2-27-04 has been considered.

Priority

The instant application and parent application 09/043061 have the same disclosure. The specification teaches isolating cells from the hippocampus of embryonic day 14, H-2Kb-tsA58 transgenic mice. All cells of the mice are conditionally immortal because they are genetically modified to have a temperature-sensitive oncogene (tsA58) (pg 9, lines 1-15). MHP36 are a clonal cell line "derived" from H-2Kb-tsA58 hippocampal cells (Example 6, pg 24, last 12 lines). The specification teaches MHP15 and MHP36 cells are nestin positive on pg 20, Example 4. The specification teaches administering MHP36 intracerebrally in Example 6, pg 24, and administering MHP15 intracerebrally in Example 8, pg 27. The cells were cultured in permissive conditions (immortal), removed from permissive conditions (non-permissive, allows differentiation) and grafted into rats (para. bridging pg 24-25). The rats are a model for cognitive deficit (pg 25, 1st para. and para. bridging pg 9-10). Pluripotent neuroepithelial cells can be isolated from humans at an equivalent developmental stage, for example at about 8 weeks (pg 13, lines 14-16).

This application repeats a substantial portion of prior Application No. 09/537617, filed 3-29-00, now US Patent 6,569,421, and adds and claims additional disclosure not presented in the prior application. Since this application names an inventor or inventors named in the prior application, it may constitute a continuation-in-part of the prior application. Should applicant desire to obtain the benefit of the filing date of the prior application, attention is directed to 35 U.S.C. 120 and 37 CFR 1.78.

Claim Rejections - 35 USC § 112

Written Description

Claims 57, 58, 60-62 and 64 remain rejected and claims 76-86 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record.

New Matter

Restoring cognitive function as in new claims 76 and 85 is found on pg 10, 1st full paragraph.

The temperature-sensitive oncogene, specifically the temperature-sensitive simian virus 40 large T antigen gene under the control of an interferon-inducible H-2Kb promoter that causes the cells to be immortal at 33° C and differentiate at 39° C as in new claims 77-81 and 83-85 is found on pg 9, lines 1-11.

The phrase "a disorder associated with damage to, or loss of, brain cells in a mammal" in claims 57, 81 and 85 is new matter. Support cannot be found on pg 1, lines 25-36, pg 2, lines 1-10 and 14-24, pg 5, lines 32-36, pg 6, pg 7, lines 1-7, pg 9, lines 1-15 and 30-36, pg 10, lines 1-36, pg 12, lines 10-23, pg 14, lines 5-11 and 29-32, pg 17, lines 21-36, pg 18, pg 19, lines 1-32, pg 20, lines 27-36 and pg 21, lines 1-8.

The phrase "wherein said cells are immortal prior to said transplanting and differentiate after said transplanting" in claim 57 is new matter. Support cannot be found on pg 1, lines 25-36, pg 2, lines 1-10 and 14-24, pg 5, lines 32-36, pg 6, pg 7,

lines 1-7, pg 9, lines 1-15 and 30-36, pg 10, lines 1-36, pg 12, lines 10-23, pg 14, lines 5-11 and 29-32, pg 17, lines 21-36, pg 18, pg 19, lines 1-32, pg 20, lines 27-36 and pg 21, lines 1-8.

The phrase "wherein said transplanting improves brain function of said mammal" in claims 57 and 81 is new matter. Support cannot be found on pg 1, lines 25-36, pg 2, lines 1-10 and 14-24, pg 5, lines 32-36, pg 6, pg 7, lines 1-7, pg 9, lines 1-15 and 30-36, pg 10, lines 1-36, pg 12, lines 10-23, pg 14, lines 5-11 and 29-32, pg 17, lines 21-36, pg 18, pg 19, lines 1-32, pg 20, lines 27-36 and pg 21, lines 1-8.

The phrase "a disorder associated with damage to, or loss of, brain cells in the hippocampus of said mammal" in claim 58 is new matter. Support cannot be found on pg 1, lines 25-36, pg 2, lines 1-10 and 14-24, pg 5, lines 32-36, pg 6, pg 7, lines 1-7, pg 9, lines 1-15 and 30-36, pg 10, lines 1-36, pg 12, lines 10-23, pg 14, lines 5-11 and 29-32, pg 17, lines 21-36, pg 18, pg 19, lines 1-32, pg 20, lines 27-36 and pg 21, lines 1-8.

The phrase "wherein said transplanting improves cognitive function of said mammal" in claims 57 and 81 is new matter. Support cannot be found on pg 1, lines 25-36, pg 2, lines 1-10 and 14-24, pg 5, lines 32-36, pg 6, pg 7, lines 1-7, pg 9, lines 1-15 and 30-36, pg 10, lines 1-36, pg 12, lines 10-23, pg 14, lines 5-11 and 29-32, pg 17, lines 21-36, pg 18, pg 19, lines 1-32, pg 20, lines 27-36 and pg 21, lines 1-8.

Treating humans as in claims 82 and 86 is new matter. Support cannot be found on pg 1, lines 25-36, pg 2, lines 1-10 and 14-24, pg 5, lines 32-36, pg 6, pg 7, lines 1-7, pg 9, lines 1-15 and 30-36, pg 10, lines 1-36, pg 12, lines 10-23, pg 14, lines 5-11 and

29-32, pg 17, lines 21-36, pg 18, pg 19, lines 1-32, pg 20, lines 27-36 and pg 21, lines 1-8.

When adding a new phrase to a claim, please specifically point out where each phrase is supported by the specification by page and line number. Generically citing pg 1, lines 25-36, pg 2, lines 1-10 and 14-24, pg 5, lines 32-36, pg 6, pg 7, lines 1-7, pg 9, lines 1-15 and 30-36, pg 10, lines 1-36, pg 12, lines 10-23, pg 14, lines 5-11 and 29-32, pg 17, lines 21-36, pg 18, pg 19, lines 1-32, pg 20, lines 27-36 and pg 21, lines 1-8, as supporting 10 new claims and the amendments in claims 57 and 58 is inadequate. If an explanation of why the phrase in the specification relates to the claim as a whole, please provide a reasoned statement correlating the teachings in the specification to the claim as a whole. For example, the specification as a whole does not support using any nestin-positive, neuroepithelial cells as newly amended because the specification only taught using hippocampal neuroepithelial cells. Nor does the specification support improving any "brain function" as newly amended by adding neuroepithelial cells because the specification only taught using a model of cognitive function (pg 10).

Written Description

The rejection of claims 57, 58, 60-62 regarding transplanting "human" pluripotent, nestin-positive neuroepithelial cells has been withdrawn because the term "human" has been deleted.

Claims 82 and 86, directed toward treating a cognitive function in a human using pluripotent, nestin-positive neuroepithelial cells, lack written description.

Since the time of filing Gray (August 29, 1999, Philosophical Transactions of the Royal Soc. London, Vol. 354, No. 1388. pg 1407-1421) taught "[i]f primary embryonic tissue is used as the source of neural transplants... ...it is vital to take the tissue from the embryonic brain at a time at which the requisite cells have already differentiated into their final phenotype but have not yet sprouted axons; take the tissue too early, and it is ineffective; take it too late and the cells die" (pg 1408, col. 2, lines 15-20). Therefore adequate numbers of cells having a desired final phenotype is essential to the invention. Gray specifically states treating hippocampal damage requires human fetal hippocampal tissue isolated from 15 week old embryos (pg 1409, lines 9-16). Therefore, fully differentiated hippocampal cells not yet having axons are essential to the invention and are equivalent to those isolated from a human fetal brain at 15 weeks of gestation.

Renfranz of record (1991, Cell, Vol. 66, pg 713-729) taught differentiation of nestin-positive pluripotent cells varied. Different nestin-positive pluripotent cells differentiated into different types of neural cells (see first line of introduction on pg 713).

Villa (2000, Exp. Neurol., Vol. 161, pg 67-84) taught that properties identifying a human neural stem cell are not well understood (pg 81, lines 1-5) and used a working definition of human neural stem cells as those expressing nestin and having the ability to self-renew. Villa taught the potential for using human neural stem cells expressing nestin and capable of self-renewing to treat humans was unknown (pg 82, col. 2, 3rd ¶, 4th sentence).

The specification taught using mouse, pluripotent, nestin-positive, hippocampal neuroepithelial cells to restore cognitive function in rats and suggested isolating pluripotent neuroepithelial cells from humans, for example at about 8 weeks (pg 13, lines 14-16). The specification does not teach cells isolated from a human fetus at 8 weeks differentiate into the desired cells equivalent to those described by Gray at 15 weeks of gestation. The specification does not teach how to control differentiation so that cells isolated from a human fetus at 8 weeks differentiates into only the desired cells and not other neural cells. The specification does not describe properties of human neural stem cells beyond nestin expression and the ability to self-renew, a generic definition of neural stem cells described by Villa, so that one of skill could determine human cells capable of treating cognitive deficit. The specification does not teach using the mouse cells to treat humans having a cognitive deficit.

An adequate written description of a method of using human, nestin-positive, neuroepithelial cells for treating a cognitive deficit requires more than a mere statement that the method is part of the invention and reference to a potential method for isolating the cells used in the method. What is required is a description of the human cells capable of treating a cognitive deficit. Thus, claiming a method of treating cognitive deficit using pluripotent, nestin-positive neuroepithelial cells in humans without defining the properties required to obtain human cells capable of treating a cognitive deficit or how to use mouse cells to treat humans is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. It is not sufficient to define the method as requiring cells having particular biological properties,

i.e. expressing nestin and pluripotent and capable of treating humans, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of human cells capable of restoring cognitive function. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Therefore, applicants did not provide adequate written description for using nestin-positive, pluripotent neuroepithelial cells for restoring a cognitive deficit in a human.

Applicants argue the examiner's interpretation of Gray is incorrect because Gray describes using fully differentiated cells. Applicants argue the specification overcomes this hurdle by implanting cells isolated prior to week 15 that become fully differentiated cells (¶ bridging pg 8-9 of response). Applicants' arguments are not persuasive. Gray states "[I]f primary embryonic tissue is used as the source of neural transplants... ...it is vital to take the tissue from the embryonic brain at a time at which the requisite cells have already differentiated into their final phenotype but have not yet sprouted axons; take the tissue too early, and it is ineffective; take it too late and the cells die." Gray specifically states treating hippocampal damage requires human fetal hippocampal tissue isolated from 15 week old embryos (pg 1409, lines 9-16). Applicants have not overcome the hurdle described by Gray by teaching how to control differentiation of cells isolated at 12 weeks of gestation once the cells implanted into the brain so that adequate numbers of fully differentiated cells having the desired function are obtained. The specification does not describe obtaining an adequate amount of fully differentiated hippocampal cells upon transplantation equivalent to those isolated from the

hippocampus of a 15-week-old human fetus. The specification does not describe how to control differentiation of cells isolated from an 8-week human fetus, which would have increased potential to become other types of cells. Without such guidance, applicants do not provide written description for the human equivalent of the mouse, nestin-positive cells capable of treating cognitive function described in the specification.

Applicants argue the declaration filed 9-30-02 states nestin-positive neuroepithelial cells can be obtained from human fetal cortex at 12 weeks gestation (pg 9, lines 4-7, of response). Applicants' argument is not persuasive. The specification does not teach how to control differentiation of such cells *in vivo* to obtain adequate numbers of cells capable of treating a cognitive deficit equivalent to those obtained at week 15 described by Gray and to avoid obtaining undesired neural cells. Furthermore, Exhibit D of the declaration filed 9-30-02 did not teach using the same method described in the specification to obtain the human cells. Isolating cells at 12 weeks of gestation in humans was not described in the specification as originally filed. The human cells in Exhibit D were isolated from the cortex and not the hippocampus as taught in the specification, which is not described in the specification. The mouse cells in the specification were obtained from transgenic mice whose genomes comprise DNA encoding the temperature sensitive gene (tsA58); however, the cells in Exhibit D were not isolated from transgenics. Finally, the human cells described in the declaration that treated cognitive deficit expressed musashil, which is not taught in the specification. As such, the human equivalent of the mouse, nestin-positive, pluripotent neuroepithelial cells does is not adequately described in the specification as originally filed because

more information than given in the specification would have been required for one of skill to obtain a human cell encoding tsA58 having the ability to restore cognitive function found in MHP36.

Applicants argue Villa supports the written description of the claimed invention. Applicants' argument is not persuasive because Villa was not available at the time of filing. Villa specifically states the potential for using human neural stem cells expressing nestin and capable of self-renewing to treat humans was unknown (pg 82, col. 2, 3rd ¶, 4th sentence). Therefore, Villa does not provide post-filing evidence that the specification as originally filed was adequate to obtain human cell capable of treating a cognitive deficit. In addition, the cells described by Villa are different than those described in the specification, and Villa did not teach using the cells to treat cognitive deficit. Overall, Villa confirms the examiner's position that it was not known how to obtain genetically modified human nestin-positive cells capable of treating humans.

Enablement

Claims 57, 58 and 60-62 remain rejected and claims 76-86 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a cognitive deficit in a rat caused by a hippocampal lesion comprising administering mouse, hippocampal, nestin-positive, pluripotent, neuroepithelial cells comprising a vector encoding tsA58 operably linked to the H-2Kb promoter to the hippocampus of the rat such that the cognitive deficit is treated, does not reasonably provide enablement for i) using any pluripotent, nestin-positive neuroepithelial cells to

treat any disorder associated with damage to, or loss of, any brain cells, ii) treating damaged brain cells by implanting genetically modified cells anywhere within the brain, iii) using nestin-positive, pluripotent, neuroepithelial cells to treat a disorder associated with damage to, or loss of, brain cells in a human, or iv) using any "conditionally immortal" cells as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

Any new enablement rejections below have been made because of the increased breadth of claim 57 and the breadth of new claims 81 and 85.

Applicants claim a method of treating a human using neural stem cells expressing nestin and capable of self-renewal, but have not linked cells having such a phenotype to the ability to treat cognitive deficits in humans.

The state of the art at the time of filing was such that it is unpredictable how to target particular areas of the brain when transplanting neural cells (Scheffler of record, 1999, Trends in Neurosci, Vol. 22, pg 348-357; ¶ bridging pg 354-355).

The hippocampal lesion/water maze model used by applicants is an assay for cognitive deficit (¶ bridging pg 9-10).

Sinden of record (1997, Neuroscience, Vol. 81, pg 599-608) taught for transplanted neural cells to restore performance in water maze tests, the cells must be CA1 cells derived from the hippocampus and highly specific to the damaged CA1 tissue (pg 601, ¶ bridging col. 1-2). For example, CA1 cells are effective, but CA3 cells

derived from the hippocampus or cells derived from other portions of the brain are not effective (pg 601, sentence bridging col. 1-2).

Since the time of filing Gray (August 29, 1999, Philosophical Transactions of the Royal Soc. London, Vol. 354, No. 1388. pg 1407-1421) taught "[i]f primary embryonic tissue is used as the source of neural transplants... ...it is vital to take the tissue from the embryonic brain at a time at which the requisite cells have already differentiated into their final phenotype but have not yet sprouted axons; take the tissue too early, and it is ineffective; take it too late and the cells die" (pg 1408, col. 2, lines 15-20). Therefore adequate numbers of cells having a desired final phenotype is essential to the invention. Gray specifically states treating hippocampal damage requires human fetal hippocampal tissue isolated from 15 week old embryos (pg 1409, lines 9-16). Therefore, fully differentiated hippocampal cells not yet having axons are essential to the invention and are equivalent to those isolated from a human fetal brain at 15 weeks of gestation.

Renfranz of record (1991, Cell, Vol. 66, pg 713-729) taught differentiation of nestin-positive pluripotent cells varied. Different nestin-positive pluripotent cells differentiated into different types of neural cells (see first line of introduction on pg 713).

Villa (2000, Exp. Neurol., Vol. 161, pg 67-84) taught that properties identifying a human neural stem cell are not well understood (pg 81, lines 1-5) and used a working definition of human neural stem cells as those expressing nestin and having the ability to self-renew. Villa taught the potential for using human neural stem cells expressing

nestin and capable of self-renewing to treat humans was unknown (pg 82, col. 2, 3rd ¶, 4th sentence).

The specification teaches obtaining hippocampal, pluripotent neuroepithelial cells from H-2Kb-tsA58 transgenic mice, culturing the cells in "permissive" conditions (immortal), removing the cells from "permissive" conditions (cells begin to differentiate) and transplanting the cells to the CA1 area of rats with damaged CA1 tissue. The rats receiving H-2kb-tsA58 cells showed improved performance as compared to the ischemia control animal and an equivalent performance as compared to a sham control animal in the water maze test (Example 5, pg 22; pg 23, line 8; Fig. 9). The specification also teaches obtaining MHP36, a clonal cell line derived from the H-2Kb-tsA58 mouse, hippocampal neuroepithelial cells, which showed similar results (Example 6, pg 24, Fig. 10). The mouse MHP36 cell line is nestin-positive as claimed (Example 4, pg 21, lines 1-6). The specification states the cells of the invention can be isolated from humans at an equivalent developmental stage, for example at about 8 weeks (pg 13, lines 14-16).

The specification does not enable using pluripotent, nestin-positive neuroepithelial cells isolated from any part of the brain to treat damage to, or loss of, any brain cells (claims 57, 81). The specification is limited to treating damage to hippocampal cells using hippocampal, pluripotent, nestin-positive, neuroepithelial cells. Applicants have not provided any guidance that such hippocampal cells are capable of differentiating into non-hippocampal cells. Applicants have not provided any guidance that non-hippocampal, pluripotent, nestin-positive neuroepithelial cells are capable of

differentiating into hippocampal cells and capable of treating a cognitive function. Therefore, the claims should be limited to treating damage to hippocampal brain cells using hippocampal, pluripotent, nestin-positive neuroepithelial cells as in claim 85.

The specification does not enable treating a disorder caused by damaged brain cells by implanting pluripotent, nestin-positive neuroepithelial cells anywhere within the brain (claims 57, 81). This issue was raised previously by the examiner, and in response, the claims were limited to injecting hippocampal cells into the hippocampus. In view of the increased breadth of claim 57 and 81, the rejection has been revived. While the cells described in the specification migrate to damaged brain tissue, the specification does not provide any guidance that adequate numbers of cells migrate to the damaged tissue so that the tissue is treated, specifically, so that a disorder such as cognitive deficiency is treated. In view of the unpredictability of how to use pluripotent, nestin-positive cells to treat brain damage, the specification does not provide adequate guidance for one of skill to determine how to treat brain damage by injecting the cells anywhere in the brain. It would have required one of skill undue experimentation to determine how to obtain adequate numbers of cells to migrate to the damaged tissue so that a disorder caused by the damage was treated.

The specification does not enable using human nestin-positive, pluripotent, neuroepithelial cells to treat a disorder associated with damage to, or loss of, brain cells (85 and 86). The specification taught using mouse, pluripotent, nestin-positive, hippocampal neuroepithelial cells to restore cognitive function in rats and suggested isolating pluripotent neuroepithelial cells from humans, for example at about 8 weeks

(pg 13, lines 14-16). The specification does not teach cells isolated from a human fetus at 8 weeks differentiate into the desired cells equivalent to those described by Gray at 15 weeks of gestation. The specification does not teach how to control differentiation so that cells isolated from a human fetus at 8 weeks differentiate into only the desired cells and not other neural cells. The specification does not describe properties of human neural stem cells beyond nestin expression and the ability to self-renew, a generic definition of neural stem cells described by Villa, so that one of skill could determine how to differentiate human cells into cells capable of treating cognitive deficit.

The specification does not enable treating humans using pluripotent, nestin-positive, neuroepithelial cells (82). The specification discloses mouse cells capable of treating rats, but does not teach the cells are capable of treating humans. The specification did not teach how to obtain human, pluripotent, nestin-positive neuroepithelial cells capable of treating a disorder caused by brain damage for reasons set forth above. Therefore, the specification does not teach the cells that are capable of treating humans as claimed. Without such guidance, it would have required one of skill undue experimentation to determine the cells and parameters required to treat humans using pluripotent, nestin-positive, neuroepithelial cells as claimed.

The specification does not enable using any "conditionally immortal" cells as broadly claimed (57) or any cells merely comprising a "temperature-sensitive simian virus 40 large T antigen gene" (81). The specification is limited to temperature sensitive mutants that are expressed upon being transplanted into a host having an increased temperature. The only means described in the specification in which cells are immortal

prior to transplanting and differentiate after transplanting (claim 57) is by using a genetic construct encoding tsA58. The specification does not teach any other proteins that provide conditional immortality. Expression of the tsA58 must be inducible, e.g. under the control of an inducible promoter. The specification taught using the interferon-inducible H-2Kb promoter but did not teach using constitutive promoters as encompassed by the claims. It would have required one of skill undue experimentation to determine how to make or use any other "conditionally immortal" cells as claimed or to using cells comprising DNA encoding tsA58 under the control of a promoter other than the interferon-inducible H-2Kb promoter such that the cells differentiated upon being transplanted into the brain.

Applicants argue Scheffler does not correlate to the claimed invention because Scheffler refers to a study that uses differentiated cells. Applicants point to the declaration filed 10-7-02 (pg 10 of response). Applicants' arguments are not persuasive. Scheffler clearly states targeting neural cells to the desired tissue in the brain was unpredictable. A mere statement that the cells do not require targeting particular areas of the brain without evidence or scientific reasoning is inadequate to overcome the rejection. While the specification and the declaration teach the cells migrate to damaged tissue (pg 11, 1st full ¶ of response), nowhere in the specification or in the declaration do applicants teach the amount of cells that migrate to damaged tissue is adequate to treat a disorder caused by brain damage. No evidence or correlative evidence indicating the number of cells that migrate to a site of brain damage would be adequate to treat a disorder. In addition, the cells used in the declaration

were not described in the specification as originally filed. Therefore, contrary to applicants' statement on pg 11, ¶ 2, last sentence of the response, the specification is not "replete" with teachings that cells migrating to damaged tissue are capable of achieving repair.

Applicants argue cells from the hippocampal region can repair other parts of the brain (pg 11, 3rd ¶). Applicants' argument is not persuasive. No evidence can be found in Exhibit B, pg 2-5, that cells migrated in adequate numbers to cause repair. No evidence can be found that the cells in Exhibit B were prepared the same as those described in the specification. In particular, pg 4, ¶ 47, of Exhibit B merely discusses migration and does not state adequate numbers of cells migrated to the site of tissue damage such that the cognitive deficit was treated.

Applicants point to Snyder, but it is unclear how applicants believe Snyder can be used to support the claimed invention. Snyder was not available at the time of filing and did not teach treating a disorder caused by brain damage by injecting pluripotent, nestin-positive cells anywhere in the brain. Snyder teaches no more than applicants, i.e. pluripotent, nestin-positive cells migrate to tissue damage in the brain, but does not teach treating disorders using cells that have migrated to the damaged tissue in the brain.

Applicants point to Exhibit D in the declaration filed 10-7-02 (pg 12 of response), which has already been found not persuasive. While the specification states human cells are obtained from a stage equivalent to day 14 or 15 in mice, i.e. about 8 weeks of gestation in humans, the declaration taught isolating human cells at 12 weeks of

gestation. 12 weeks of gestation in humans is not equivalent to day 14 or 15 of gestation in mice as described in the specification. Secondly, the human cells were isolated from the cortex, which was not taught in the specification. Thirdly, the mouse cells in the specification were obtained from transgenic mice while the human cells in the declaration were not. The specification does not teach how to make equivalent cells from transgenic humans, how to incorporate a temperature sensitive gene into the genome of human, pluripotent, neuroepithelial cells or how to obtain levels of tsA58 expression found in mouse MPH36 cells required for temperature sensitivity using transfection methods in human cells. Finally, according to the declaration, the human cells that treated cognitive deficit expressed musashil, which is not taught in the specification. As such, the human equivalent of the mouse, nestin-positive, pluripotent neuroepithelial cells does is not adequately taught in the specification as originally filed because more information than given in the specification would have been required for one of skill to obtain a human cell encoding tsA58 having the ability to restore cognitive function found in MHP36. Therefore, applicants did not provide adequate guidance for one of skill in the art at the time of filing to obtain human, nestin-positive, pluripotent neuroepithelial cells claimed capable of the sole disclosed use for such cells, restoring cognitive function. It would have required one of skill undue experimentation to determine that musashil expression, isolation from the cortex and 12 weeks of gestation were required to obtain the human cells claimed capable of treating a cognitive deficit as claimed. Therefore, the specification did not enable one of skill in the art at the time of filing to use human cells to treat a cognitive deficit as claimed.

Applicants point to Sinden (1997) of record, and state that Sinden (1997) is merely characterizing the prior art and not conditionally immortal cells as claimed (pg 12 2nd full ¶ of response). Applicants' argument is not persuasive. Sinden establishes the fact that the cells must be "highly specific" to treat damaged brain tissue. Applicants have not provided adequate guidance that any brain cell can treat any area of the brain.

Applicants argue routine screening would be required to obtain human, nestin-positive neuroepithelial cells (pg 13 of response). Applicants' argument is not persuasive. Applicants found the marker "musashil" was essential to identify the desired human equivalent cells (declaration filed 10-27-02); however, the specification did not teach the marker "musashil" was required to obtain the desired human equivalent cells. Therefore, more than routine screening would have been required to obtain the human, pluripotent, nestin-positive neuroepithelial cells capable of treating a disorder caused by brain damage.

Applicants argue other genes besides tsA58 can be used to make a cell conditionally immortal (¶ bridging pg 13-14). Applicants' argument is not persuasive. The specification does not teach how to induce expression of other proteins so that differentiation occurs upon implanting the cell into the brain. Applicants point to an oncogene that can make a cell conditionally immortal; however, it cannot be envisioned how to use an oncogene to induce differentiation upon implanting the cell into the brain.

Applicants refer to what one of skill would have known about musashi 1 expression, which apparently is equivalent to "musashil" (pg 14, 1st full ¶ of response). Applicants' argument is misplaced because musashi 1 was not known at the time of

filing. If applicants' are attempting to argue that musashi 1 expression is not essential to obtain human equivalent cells, applicants must provide evidence that all pluripotent, nestin-positive neuroepithelial cells express musashi 1. It appears that applicants used "musashi 1" to further limit the types of human cells isolated.

Double Patenting

The rejection under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 6,569,421 in view of Snyder of record (US Patent 5,958,767, Sept. 28, 1999) has been withdrawn in view of the terminal disclaimer filed.

The provisional rejection of claims 57, 58 and 60-62 and 76-86 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of copending Application Nos. 09/672,606 has been withdrawn because the application has been abandoned.

Claims 57, 58 and 60-62 remain provisionally rejected and claims 76-86 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of copending Application Nos. 10/342692 and 10/376119. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims would anticipate the claims of '692 and '119. Applicants' statement that the claims are not obvious over the claims of '692 and '119 are unfounded.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at 571-272-0738.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on 571-272-0804.

The official fax number for this Group is (703) 872-9306.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER